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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,320	02/21/2006	Braj Bhushan Lohray	GRT/4062-162	5297

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EXAMINER	
WEGERT, SANDRA L	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,320	LOHRAY ET AL.	
	Examiner	Art Unit	
	SANDRA WEGERT	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *19-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/29/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, and/or Claims

The Information Disclosure Statement, sent 29 April 2005, has been entered into the record. Applicants' election of Invention I (Claims 1-18) in the Paper of 14 April 2008, is acknowledged. Applicants traversed the Restriction (14 April 2008), arguing essentially that the special technical features taught in the Disclosure are not found in the document cited as prior art in the Restriction requirement (Garcia, et al, 1995, of record). The examiner agrees that some of the special technical features taught in the disclosure are not found in the Garcia reference. However, the independent claim of the first invention (Claim 1) does not recite those special technical features that make a contribution over the prior art. In fact, every part of Claim 1 is explicitly demonstrated in the prior art reference. Thus, the Garcia reference *can* appropriately be used to break Unity. See MPEP § 1850 (I), 3rd paragraph.

Claims 19-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected Inventions, there being no allowable generic or linking claim.

Claims 1-18 are under examination in the Instant Application.

Claim Rejections/Objections

Claim Rejections- 35 USC § 102

The following is a quotation of the appropriate paragraph of 35 U.S.C. 102 that forms the basis for the rejections under this sect ion made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 11-17 are rejected under 35 U.S.C. 102(b) as being unpatentable over Garcia, et al, (1995, Biotecnologia Aplicada, 12(3): 152-155). Garcia, et al disclose methods of high level recombinant expression of human Interferon (IFN)-alpha 2b using the yeast *Pichia pastoris* as host. The nucleic acid sequence encoding human IFN-alpha 2b in Garcia, et al is the same as SEQ ID NO: 1 of the instant disclosure. It differs from the claimed nucleic acid of SEQ ID NO: 3 by two bases, but encodes the same polypeptide (see the Obviousness rejection below applied over claims 2 and 3). The Pichia pastoris yeast of Garcia, et al was grown in conventional phosphate buffers (such as "BGY") with defined salt media, used peptones as a nitrogen source, was supplemented in culture with glucose and glycerol, was additionally supplemented with methanol, and grown at typical pH ranges and temperatures for yeast, such as described in claim 15 (p. 153, paragraphs 1-7). Garcia, et al obtained approximately the same yield of protein (or sometimes slightly higher) as that shown in the instant application (400 mg/L of interferon from a biomass of 35-60 g/L of yeast, see Table 1, and 7% by-weight expression from p. 154).

Claim Rejections-35 USC § 103(a), Obviousness.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Garcia, et al (1995, Biotecnologia Aplicada, 12(3): 152-155) in view of Streuli, et al (1981, Science, 209: 1343-1347, of record).

Garcia, et al disclose methods of high level recombinant expression of human IFN-alpha 2b using the yeast *Pichia pastoris* as host and SEQ ID NO: 1 of the instant disclosure. Claim 2 recites use of the human IFN-alpha 2b gene from human leucocytes (SEQ ID NO: 3). Garcia, et al do not teach SEQ ID NO: 3. Streuli, et al disclose SEQ ID NO: 3 (as Accession No. J00207) and describe it as being derived from human leukocytes (Table 2).

It should be kept in mind that SEQ ID NO: 3 encodes the *same polypeptide* as the variant of human IFN that is not produced by leukocytes, with only two nucleotide differences. Thus, the use of SEQ ID NO: 3 can be seen as an arbitrary choice of several available human IFN-alpha 2b variants, that does not contribute in any way to optimization of protein production by *Pichia pastoris* (as described above). Since Garcia, et al suggest that *Pichia pastoris* be used for high-level heterologous expression of proteins (p. 153, 1st paragraph) and also due to the high level of expression of human IFN-alpha 2b in these cells, and because Streuli, et al found no difference in expression of leukocyte IFN-alpha 2b versus that from other cells, it would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to use *Pichia pastoris* cells to express the leukocyte IFN sequence of SEQ ID NO: 3. The skilled artisan would be motivated to do so because both Garcia, et al and Streuli, et al teach that

IFN-alpha 2b has antiviral activity (p. 152 and 2848, respectively) and that therefore high-level expression is a worthwhile goal (Garcia, et al, p. 154). There would be a reasonable expectation of success, since *Pichia pastoris* is described as an ideal host for heterologous expression of proteins (Garcia, et al, p. 153, 1st paragraph).

Claims 3-10 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garcia, et al in view of Escary, et al (2002, EP 1236800A1, of record).

Garcia, et al teach methods of high level recombinant expression of human IFN-alpha 2b using the yeast *Pichia pastoris* as host and SEQ ID NO: 1 of the instant disclosure. The recombinant INF-alpha-2b was purified from the yeast culture by harvesting the cells, breaking them using mechanical means, and washing the solution over sequential columns comprising the antibody CB-IFN A 2.4 (p. 153, paragraph 8). Garcia et al do not teach use of PCR to clone the human IFN alpha 2b gene sequence, or the chromatography purification steps of claim 18.

Escary, et al teach the use of PCR to produce human IFN-alpha 2b. Escary, et al also disclose primers used for PCR cloning of 9 different human IFN-alpha 2b variants based on SNP's found in the human population, including the disclosed primer pairs SEQ ID NO: 5 (corresponding to SEQ ID NO: 26 in the Escary, et al document) and SEQ ID NO: 4 (corresponding to SEQ ID NO: 19 in Escary, frame-shifted by one codon). Furthermore, Garcia, et al teach use of P. pastoris GS115 (called MP36, p. 154), use of the vector pIFNPP (Fig 1), and use of the AOX(1) promoter to control expression (p. 154, 1st paragraph) The transformed yeast cell used in Garcia, et al was a His auxotroph (p. 153, paragraph 5).

Therefore, it would have been obvious for one of skill in the art to combine the teachings of Garcia, et al and Escary, et al, to produce human IFN alpha-2b DNA by PCR and purify the recombinantly-produced polypeptide by chromatography. Since Garcia, et al suggest that *Pichia pastoris* be used for high-level heterologous expression of proteins (p. 153, 1st paragraph), and since one of skill in the art can design primers to express any gene, and also because Escary, et al, designed approximately 20 different primers for targeted cloning, it would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to use a variety of primers to express the IFN sequence of SEQ ID NO: 3. Likewise, referring to Claim 18, Escary et al recite methods of chromatography used to purify variants of IFN besides human IFN-alpha 2b of SEQ ID NO: 3. The authors disclose several methods of IFN purification including the sequential chromatography steps listed in claim 18 of ion exchange followed by gel filtration (paragraphs 0440 and 0458-0463). Since Garcia, et al suggest that *Pichia pastoris* be purified (p. 153), and since one of skill in the art can use chromatography to purify almost every protein, and because Escary, et al, purified several variants of human IFN-alpha 2b, it would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to be able to purify SEQ ID NO: 3 using the methods described in Escary, et al.

Conclusion: Claims 1-18 are rejected for the reasons recited above.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Manjunath Rao, can be reached at (571) 272-0939.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (in USA or CANADA) or 571-272-1000.

/SLW/
14 July 2008

/Elizabeth C. Kemmerer/

Primary Examiner, Art Unit 1646